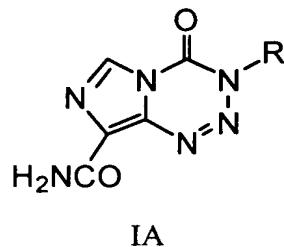
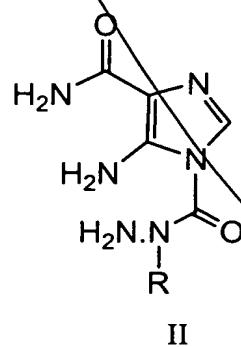


What is claimed is

1. A process for the preparation of a compound of the formula IA



wherein R is an alkyl group having from 1 to 6 carbon atoms, which comprises reacting a compound of the formula II



wherein R is described above, with an oxidation/cyclization agent in the presence of an iodide, in an inert medium, under an inert atmosphere and at a temperature and 15 for a time sufficient enough to produce a compound of the formula IA, wherein said iodide is soluble in said inert medium.

20

2. The process of claim 1 wherein R is an alkyl group having 1 to 4 carbon atoms.

3. The process of claim 1 wherein said oxidation/cyclization agent is selected from the group consisting of:

a) periodic acid,  
b) iodine/potassium iodate,  
c) bromine,

d) chlorine; and

e) a reagent that oxidizes  $\text{NH}_2$  to  $\text{NZ}$ , where Z represents, Oxygen, (H, Hal), or  $\text{Hal}_2$ , and wherein Hal is chlorine, bromine or iodine.

*P-A 4*  
4. The process of claim 1 wherein said iodide is a quarternary ammonium iodide and said inert medium is an inert organic solvent.

5. The process of claim 4 wherein said iodide is selected from the group consisting of  $\text{Bu}_4\text{NI}$  and  $\text{KI}$ .

10

6. The process of claim 4 wherein said inert organic solvent is selected from the group consisting of:

a) an amide;

b) an acyclic ether;

c) a cyclic ether;

d) an alkyl alkanoate wherein the alkyl group has 1 to 4 carbon atoms and the alkanoate group has 2 to 4 carbon atoms;

e) a halogenated hydrocarbon and

f) mixtures thereof.

15

7. The process of claim 6 wherein the organic solvent is selected from the group consisting of:

a) DMF;

b) t-butyl-methyl ether;

c) THF;

d) acetonitrile;

e) methylene chloride;

f) toluene; and

g) mixtures of the above solvents,

25

30

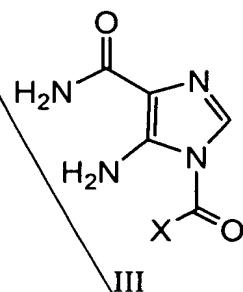
8. The process of claim 7 wherein the reaction takes place at a temperature of about (-)20°C to about (+) 70°C and under a nitrogen atmosphere.

9. The process of claim 6 wherein:

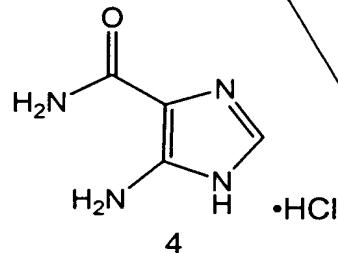
- the organic solvent is a 50/50 mixture of THF/CH<sub>3</sub>CN;
- the oxidation/cyclization agent is H<sub>5</sub>IO<sub>6</sub>;
- the iodide is Bu<sub>4</sub>NI and
- the reaction takes place at a temperature of about 0°C to about 60°C.

*Recd  
5  
A6*

10. A process for preparing a compound of the formula III:



which comprises reacting a compound of the formula 4:



15

with a compound of the formula X-CO-Y, wherein each of X and Y is the same or different leaving group, to yield a compound of the formula III.

11. The process of claim 10 wherein X of said compound X-CO-Y is selected from the group consisting of

- phenyloxy;
- 2-naphthoxy and
- substituted phenyloxy,

and wherein Y of said compound X-CO-Y is selected from:

25

- chlorine,
- bromine, or

c) iodine.

12. The process of claim 11 wherein the substituents on said substituted phenoxy group are selected from the group consisting of:

5           a) nitro;  
              b) pentafluoro;  
              c) chlorine;  
              d) bromine;  
              e) iodine, and  
10           f) combinations of the above.

13. The process of claim 10 wherein said reaction of the compound of the formula 4 with a compound of the formula X-CO-Y is performed in the presence of an acid binding agent, in an inert organic solvent, under an inert atmosphere and at a temperature of about (-) 20°C to about (+) 50°C.

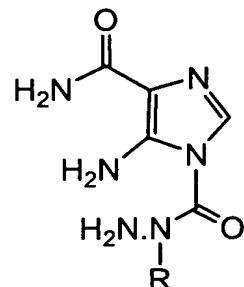
14. The process of claim 13 wherein said acid binding agent is a tertiary amine.

20           15. The process of claim 13 wherein the organic solvent is selected from the group consisting of

25           a) an amide;  
              b) an acyclic ether;  
              c) a cyclic ether;  
              d) an alkyl alkanoate wherein the alkyl group has 1 to 4 carbon atoms and the alkanoate group has 2 to 4 carbon atoms;  
              e) a halogenated hydrocarbon; and  
              f) mixtures thereof.

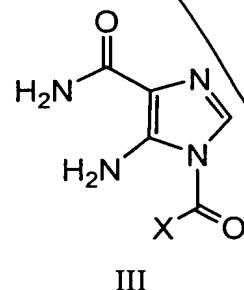
*PA 7*

16. A process for the preparation of a compound of the formula II:



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wherein R is an alkyl group having from 1 to 6 carbon atoms, comprising, reacting a compound of the formula III:



10

wherein X is a leaving group of the type that activates its adjacent carbonyl group towards nucleophiles, with an alkylhydrazine having from 1 to 6 carbon atoms.

15

17. The process of claim 16 wherein said alkylhydrazine is R-NH-NH<sub>2</sub>, wherein R is an alkyl group having 1 to 4 carbon atoms.

18. The process of claim 16 wherein the reaction takes place in an inert organic solvent selected from the group consisting of:

20

- a) a non-nucleophilic amine and
- b) an ether; and
- c) mixtures thereof.

19. The process of claim 16 wherein X is selected from the group consisting of:

- a) phenoxy;
- b) 2-naphthoxy and
- 5 c) substituted phenoxy, wherein the substituents are electron withdrawing.

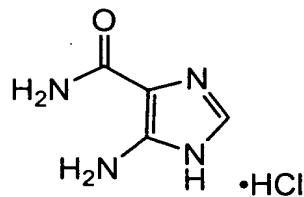
10 20. The process of claim 19 wherein said substituents are selected from the group consisting of:

- a) 2-nitro;
- b) 4-nitro;
- c) pentafluoro;
- d) chlorine and
- e) bromine.

15 21. ~~The process of claim 17 wherein said alkylhydrazine is a 1-alkyl derivative of 5-amino-4-(aminocarbonyl)-1H-imidazole-1-carboxylic acid hydrazide wherein the alkyl group contains 1 to 6 carbon atoms.~~

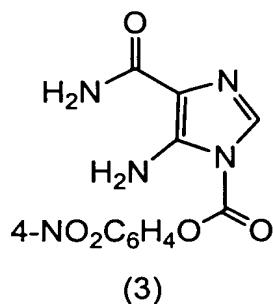
20 22. ~~The process of claim 21 wherein said alkylhydrazine is 5-amino-4-(aminocarbonyl)-1H-imidazole-1-carboxylic acid 1-methylhydrazide.~~

23. The process of claim 14 wherein compound 4:

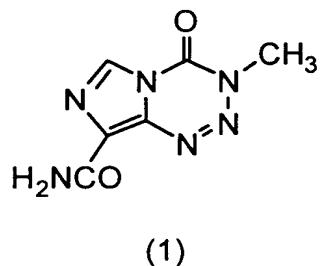


25 4

30 is reacted with 4-nitrophenyl chloroformate, in the presence of triethyl amine, said reaction taking place in methylene chloride solvent, under a nitrogen atmosphere and at a temperature of about (-)20°C to about (+) 50°C to yield compound (3):

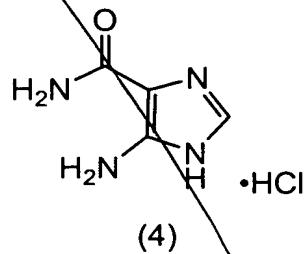


24. A process for preparing temozolomide (1):



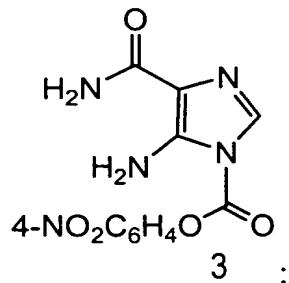
comprising:

a) reacting compound 4:



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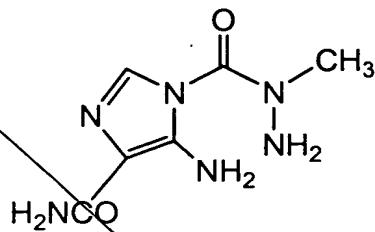
with 4-nitrophenyl chloroformate in the presence of triethylamine in  $\text{CH}_2\text{Cl}_2$  under a nitrogen atmosphere at about 25°C to obtain compound (3):



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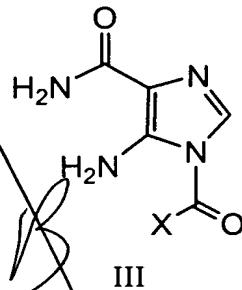
b) reacting compound (3) with methylhydrazine in DMF at about 0°C to obtain compound (2):

39  
cont



5 , and  
c) reacting compound (2) with  $\text{Bu}_4\text{NI}$  in a 50/50 mixture of  
10 THF/CH<sub>3</sub>CN, at a temperature of about (+) 60°C for a time of about zero to sixty  
minutes, followed by the cooling of the reaction mixture to about (+) 25°C and the  
addition of H<sub>5</sub>IO<sub>6</sub> and stirring for about 10 to about 60 minutes to obtain  
15 temozolomide (1).

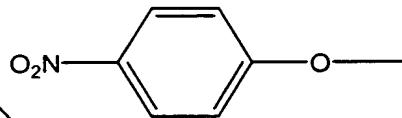
25. A compound of the formula:



15 or an active ester thereof, wherein X is a leaving group of the type that activates its  
20 adjacent carbonyl group towards nucleophiles.

26. The compound of claim 25 wherein X is OH, said compound being 5-  
20 amino-4-(aminocarbonyl)-1H-imidazole-1-carboxylic acid.

27. The compound of claim 25 wherein X is



said compound being 1-(4-nitrophenyl)-5-amino-4-(aminocarbonyl)-1H-imidazole-1-carboxylate.

5

28. The compound of claim 25 wherein X is  $-\text{N}(\text{CH}_3)\text{-NH}_2$ , said compound being 5-amino-4-(aminocarbonyl)-1H-imidazole-1-carboxylic acid-1-methylhydrazide.